Visual hallucinations in neurological and ophthalmological disease: pathophysiology and management

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Abstract

Visual hallucinations are common in older people and are especially associated with ophthalmological and neurological disorders, including dementia and Parkinson's disease. Uncertainties remain whether there is a single underlying mechanism for visual hallucinations or they have different disease-dependent causes. However, irrespective of mechanism, visual hallucinations are difficult to treat. The National Institute for Health Research (NIHR) funded a research programme to investigate visual hallucinations in the key and high burden areas of eye disease, dementia and Parkinson's disease, culminating in a workshop to develop a unified framework for their clinical management. Here we summarise the evidence base, current practice and consensus guidelines that emerged from the workshop.

Irrespective of clinical condition, case ascertainment strategies are required to overcome reporting stigma. Once hallucinations are identified, physical, cognitive and ophthalmological health should be reviewed, with education and self-help techniques provided. Not all hallucinations require intervention but for those that are clinically significant, current evidence supports pharmacological modification of cholinergic, GABAergic, serotonergic or dopaminergic systems, or reduction of cortical excitability. A broad treatment perspective is needed, including carer support. Despite their frequency and clinical significance, there is a paucity of randomised, placebo-controlled clinical trial evidence where the primary outcome is visual hallucination improvement. Key areas for future research include the development of valid and reliable assessment tools for use in mechanistic studies and clinical trials, transdiagnostic studies of shared and distinct mechanisms and when and how to treat visual hallucinations.

Introduction

Visual hallucinations (VH) and closely-related visual perceptual symptoms (Table 1) are common in degenerative diseases of the brain and eye, and their prevalence varies depending on the condition and symptom type. The three predominant clinical contexts in which VH occur as repeated episodes over a prolonged course are the (i) dementias, (ii) Parkinson's disease (PD), both in its early stages and after progression to PD dementia (PDD), and (iii) eye or visual pathway disease. Prevalence varies across different dementia subtypes with recent estimates of 55-78% in dementia with Lewy bodies (DLB), 32-63% in PDD, 11-17% in Alzheimer's disease (AD) and 5-14% in vascular dementia [1]. In DLB, well-formed and detailed VH are a core feature and incorporated into diagnostic criteria [2]. The term Charles Bonnet syndrome is used to describe VH in visual impairment due to eye or visual pathway disease, with prevalence ranging from 15-60% depending on the degree of visual loss [3]. In Parkinson's disease (PD), prevalence of VH is linked to disease duration and dopamine medication, with more than 80% cumulative prevalence over time [4].

Table 1 Glossary of terms

- Visual hallucination - visual percept not associated with a real object.
- Complex visual hallucination – subtype of visual hallucination whose content is a formed object, face, animal, figure etc.
- Visual illusion – real object perceived incorrectly. Traditionally used to refer to errors of category identity (e.g. pile of cloths seen as a cat).
- Pareidolia – specific subtype of illusion in which faces, objects etc. are perceived when viewing formless visual stimuli such as clouds, tree-bark, flames or in patterned visual stimuli such as carpets, wallpaper.
- Metamorphopsia – a subtype of illusion used to refer to errors of spatial, temporal perception (e.g. seeing a real object distorted, seeing a real object persist in time or at the wrong spatial location).
- Passage hallucination – animal or person passing (en passage), typically brief and in peripheral visual field. Characteristic of Parkinson's disease psychosis.
- Presence hallucination – sense of someone being close by or beside without an associated visual, auditory or tactile experience. Characteristic of Parkinson's disease psychosis.
- Minor hallucination – collective term used in Parkinson's disease to describe illusions, passage hallucinations and presence hallucinations.

- Multimodality hallucination – visual hallucination combined with hallucinations in other senses. Content in different modalities may be perceptually related (e.g. figure talking to you) or perceptually unrelated (disembodied voice with content unrelated to figure).
- Pseudohallucination – In neurological literature, a hallucination with insight. In psychiatric literature, a hallucination in mind's eye rather than externally projected and related to imagery.
- Full insight – In context of visual hallucinations, an understanding that the experience is not real. Insight may be absent on the first occasion a hallucination occurs because of its compelling nature but with repeated instances the experience is recognised as false.
- Partial or fluctuating insight – In context of visual hallucinations, insight is variable and frequently absent at the time the hallucination occurs. Insight may be restored in retrospect.
- Secondary delusion – a false belief related to the visual hallucination (e.g. people have been let into the house). Secondary delusions imply impaired insight.

To date, research into the mechanism and treatment of VH has focussed predominantly on these three clinical contexts, with the emergence of parallel, often contradictory, literature. Little consideration has been given to factors common to each condition or how mechanisms might interact when eye disease combines with dementia or PD. The National Institute for Health Research (NIHR) funded a 5-year research programme (SHAPED: Study of visual Hallucinations in Parkinson's disease, Eye disease and Dementia) to examine VH from a trans-diagnostic perspective focussing on these conditions and to develop a unified framework for clinical management based on combined current best practice and treatment evidence. As part of this programme, we undertook an expert-led review process of recent literature and current practice, culminating in a workshop held in April 2018 to formulate consensus guidelines for the clinical management of VH.

The underlying mechanism of visual hallucinations

The workgroup highlighted two related but distinct aspects of VH mechanism that might inform treatment. One was what brain changes occur at the time of VH (the hallucinating state); the other what brain changes are associated with a susceptibility to VH (the hallucination trait). Studies of the hallucinating state ideally require the examination of real-time brain changes coincident with VH. Transient activation of the visual association cortex has been found in Charles Bonnet syndrome around the time of onset of VH [5], while more widespread changes have been found in PD with de-activation of the visual association cortex and activation of the frontal cortex [6]. Differences in

methodology make it difficult to conclude whether this reflects a difference in the mechanism underlying the VH state in these disorders.

However, most attention has been on brain changes associated with susceptibility to VH. There are 3 mechanistic models: i) disturbed balances between top-down and bottom-up aspects of visual perception, ii) chronic deafferentation causing hyperexcitability to the cortical structures involved in vision, and iii) misattribution of internal imagery.

The first mechanism, the Perception Attentional Dysfunction (PAD) model or related variants [7-9], highlights combined impairment in distributed perceptual and attentional networks leading to disturbed balances between top-down and bottom-up processes (or priors and sensory evidence). This has especially been implicated in the aetiology of hallucinations in dementia or PD and proposes that, in combination with poor visual perception, continuous perceptual activity is under-constrained by impaired attentional focus, and that the hallucinatory element of a scene is not disconfirmed by discrepant visual input. In contrast, the second, deafferentation-hyperexcitability, model is believed to underlie Charles Bonnet syndrome, and proposes hyperexcitability secondary to chronic functional visual deafferentation, resulting in increased spontaneous activity within the higher visual cortical areas leading to VH [10]. The third model, derived from psychotic disorders, is similar to PAD in its emphasis on unbalanced generative perception but proposes that hallucinations, whatever their modality, result from a failure to correctly attribute internal events as internal due to failures in source monitoring [11].

Each model is supported by a range of evidence including: cognitive / higher visual function deficits; functional imaging of task-related activity; resting state metabolism or blood flow; cortical / white matter changes; and altered structural and functional connectivity and post-mortem neuropathology. The functional and structural changes differ between studies of VH, both within a given condition and across conditions, but may all form part of a distributed network [12, 13]. Pathology involving any part of the network may result in dysfunction that leads to VH, as shown for anatomically distinct lesion sites causing peduncular hallucinations [13].

Post-mortem evidence has the complication that changes identified may have followed the onset of VH and reflect later disease progression rather than the primary cause of VH. Nevertheless, VH during life in patients with dementia is a strong predictor of Lewy body (LB) pathology at autopsy [14, 15]. In patients with VH associated with PD and DLB, LB pathology is found in the amygdala and para-hippocampal gyrus [16], superior and lateral frontal cortex (Brodmann area 8/9), inferior/

lateral temporal cortex (Brodmann area 20, 21), inferior parietal cortex (Brodmann area 39, 40) and cingulate cortex (Brodmann area 24)[regions pooled from 17, 18].

Unlike patients with VH in the context of PD with dementia, patients with VH and relative preservation of cognition do not have prominent cortical or hippocampal LB involvement [19]. VH are also linked to higher amyloid and tau pathology in frontal, parietal and hippocampal areas [20], and patients with PD who go on to develop VH have CSF amyloid changes that suggest early AD pathology [21]. In PD without dementia, the occipital lobe is relatively free of pathology with absent LB and tau pathology and mild amyloid burden irrespective of whether patients experience VH [22].

Neurotransmitter systems and VH

In both AD and DLB, there is strong evidence for reduced cholinergic function associated with more frequent VH [23-26]. This is consistent with evidence from case series in PD and PDD suggesting improvement in VH with cholinesterase inhibitors [27-29] and improvement in VH amongst other neuropsychiatric symptoms in the secondary analysis of a large-scale clinical trial examining the effect of cholinesterase inhibitors on cognition [30].

Neurochemical studies of CSF metabolites suggest a negative correlation between the dopamine metabolite homovanillic acid (HVA) and VH in a small number of LBD patients and weak negative correlations with aspartate and taurine in AD [31]. One suggestion is that VH susceptibility is linked to a specific 3,4-dihydro-xyphenylacetic acid (DOPAC)-HVA metabolic deficit, possibly as a result of a genetic catechol-O-methyltransferase (COMT) variation. There is also evidence of reduced striatal dopamine transporter (DAT) binding in patients with PD who go on to develop VH, thought to reflect dysfunctional fronto-striatal circuitry and altered inhibitory executive function [32-35] consistent with the PAD model. This may also help explain why VH in some patients with PD/PDD improve when their dopaminergic load is dropped or partially blocked with drugs such as clozapine or quetiapine.

Post-mortem studies also highlight reductions in cholinergic and GABA activity in the absence of gross neuron or synapse loss, suggesting functional rather than structural changes may contribute to VH [36]. In PD, increased 5HT2a binding has been linked to VH in post-mortem [37] and *in vivo* neurotransmitter binding studies [38]. This may also help explain why the 5HT2a inverse agonist pimavanserin is effective treatment for hallucinations in PD.

In summary, research on the mechanism of VH has largely been confined to studies within a given clinical condition, with a paucity of trans-diagnostic research on the wider applicability of

mechanisms or interactions between them. It also remains unclear whether mechanisms proposed for complex VH also apply to related perceptual symptoms (e.g. illusions, presence hallucinations), or phenomenological variants of complex VH with full, partial/fluctuating and absent insight.

Visual hallucinations and their management

Eye disease

Charles Bonnet syndrome VH are associated with diseases affecting the retina, light transmission within the eye (e.g. cataract, corneal opacity) or visual pathways and visual cortex. They do not relate to a specific ocular pathology subtype [39] and can occur in monocular disease. Typical phenomenology includes simple hallucinations (colours and elementary shapes) geometrical patterns, disembodied faces and costumed figures [40]. Charles Bonnet syndrome risk increases in patients with severe impairment of visual acuity [3]. The frequency of VH occurrence in Charles Bonnet syndrome reduces over time, but more than 75% of patients will continue to experience hallucinations beyond 5 years after their onset [41]. Clinical impression, supported by patient surveys [42] is that Charles Bonnet syndrome is under-recognised with the fear of stigma reducing self-report. Around a third of Charles Bonnet syndrome patients have symptoms requiring clinical intervention beyond reassurance and education (negative outcome Charles Bonnet syndrome) [41]. Compared to patients with eye disease but no VH, Charles Bonnet syndrome adversely affects quality of life [43].

Current practice

For Charles Bonnet syndrome, ophthalmology services will explain symptoms, reassure and signpost for further support and self-help techniques, with some limited evidence from a case series that this may reduce VH in some people [44]. The self-help techniques aim to stop hallucinations while they occur and include eye-movements, changing lighting levels to increase visual input and alerting / distraction strategies. If clinically significant through causing distress, referral to other specialties may occur. A staged approach to treatment is used with a health screen and medication review and optimisation of vision [e.g. cataract removal, 45]. For people with VH associated with acute visual loss due to macular degeneration, a study of ranibizumab found improvement in 23%, with an association with improved visual acuity [46]. There is case-report evidence for treatment with anti-convulsants [47, 48], cholinesterase inhibitors [49], 5HT antagonists (ondansetron) [50], SSRIs [51], atypical neuroleptics [52], Yi-Gan-San [a Chinese traditional medicine with multiple neurotransmitter effects , 53] and repetitive Transcranial Magnetic Stimulation [rTMS, 54]. However, none can be recommended for routine clinical use without further evidence for their efficacy.

Parkinson's disease

VH in PD form part of a progressive spectrum of symptoms (PD Psychosis) that start with illusions, presence hallucinations and passage hallucinations and progress to formed hallucinations, typically of people and animals [55]. They are a particular challenge in PD, as treatment for motor symptoms can trigger and worsen VH. They are associated with higher mortality [56], which may be linked to antipsychotic use [57], and are a stronger predictor of nursing home placement than cognitive or motor symptoms [58]. The stigma of mental illness may lead to under-reporting [59]. VH in PD have a significant negative impact on carers, with increasing carer distress as insight into the VH becomes impaired [59]. Compared to PD patients without VH, patients with VH have reduced quality of life [60].

Current practice

The NICE 2017 guidelines for PD [61] recommend a staged approach to treatment, typically undertaken within a PD service. The starting point is a review of medical or pharmacological triggers and a delirium screen with advice on general coping strategies [62, 63]. A reduction in PD medication may be necessary while monitoring for worsening motor symptoms, dopamine withdrawal syndrome or neuroleptic malignant syndrome. Medications should be withdrawn, starting with those most likely to provoke VH, i.e., anticholinergics, amantadine, and MAO-B inhibitors, followed by dopamine agonists and COMT inhibitors. If VH persist, the cautious withdrawal of levodopa may help [64, 65]. If these strategies are not effective, antipsychotic medications may be considered [66]. Several randomised controlled trials (RCTs) have shown clozapine to be efficacious, with benefit for VH without worsening motor symptoms [67, 68]. Quetiapine is more widely used than clozapine, but there is less evidence of efficacy [69-72]. Pimavanserin, a novel antipsychotic with potent inverse agonist activity on the 5HT2A receptor, has emerged as a new potential therapy, with two positive RCTs. Meltzer et al [73] reported reduced VH, and Cummings et al. [74] reported improvements on psychosis scores and caregiver stress. Pimavanserin is licensed as a treatment for PD psychosis in the US. Rivastigmine and donepezil are used to treat cognitive impairment in PD and may also help reduce VH [27-29], although to date there are no RCTs of cholinesterase inhibitors using VH as a primary endpoint.

Dementia

VH in dementia tend to be people / children, animals or objects [75]. Around 50% of patients are significantly distressed by their experiences, with fear and anger being the most common responses [76]. As core defining features of DLB, they are likely to be present at the point of diagnosis, contrasting with AD where VH occur in later stages of cognitive decline, 5-6 years after the onset of

dementia [77]. VH are associated with increased likelihood of nursing home placement [78]. As in PD, carer impact increases when patient insight becomes impaired [59].

Current practice

VH are managed within dementia services in the wider context of neuropsychiatric symptoms. A staged approach is used with a physical health review, excluding delirium and other medical conditions that can cause VH, and medication review to reduce / stop drugs which may cause or exacerbate VH. Antipsychotics may have benefit [79] but potential adverse effects of severe antipsychotic sensitivity and mortality mean that use in LBD should be cautious. There is some evidence cholinesterase inhibitors reduce neuropsychiatric symptoms, including VH [30]. High dose cholinesterase inhibitors have been shown to reduce the frequency of VH in LBD but with increased side effects, needing careful titration under expert supervision [80]. A study of memantine found reduced hallucinations (which, although not subdivided by hallucination modality, would have mainly been VH) in DLB after 24 weeks treatment [81]. Transcranial magnetic stimulation and transcranial direct stimulation have been suggested as approaches for VH in LBD, but studies to date have not shown benefit [82].

Co-morbid disease

Studies of VH in PD or dementia typically exclude patients with eye disease so there is limited data on the prevalence, phenomenology or management of VH in the context of co-morbid eye disease. Eye disease may result in an earlier onset of VH in dementia, resulting in the misdiagnosis of AD as DLB [83]. Some patients presenting with Charles Bonnet syndrome to ophthalmology clinics may have unrecognised dementia characterised by partial or fluctuating insight into VH [84]. Case report evidence suggests that optimising vision may help reduce VH in dementia [85].

Discussion

The absence of an overarching model for VH in different disorders or evidence-based treatments limited the scope of the recommendations the workgroup could make. The focus of the NIHR programme on PD, dementia and eye disease also meant that VH in other clinical and non-clinical contexts were not covered (see Table 2). However, the consensus view was that where treatment was indicated for these other contexts, similarities in current practice across the core disorders covered allowed formulation of a common framework for clinical management likely to be of relevance to all conditions. Below we highlight key considerations, the general framework for managing VH and related symptoms, and areas for future research.

Table 2 Visual hallucinations in wider clinical and non-clinical context

Condition	Key features
Parkinson's disease	Occurs throughout PD from early stage disease without cognitive impairment to PDD (see above). Other hallucination modalities can be involved in later stages.
Charles Bonnet Syndrome	Eye or visual pathway disease (see above).
Dementia	Includes AD, DLB, PDD, AD, VaD (see above). Other hallucination modalities can be involved.
Co-morbid disease	Eye and neurodegenerative disease combined (see above).
Schizophrenia / bipolar disorder	Visual hallucinations are less prevalent than auditory hallucinations in schizophrenia and other psychoses [86]. VH in these conditions rarely occur without auditory hallucinations during course of the illness and are typically interspersed with unimodal auditory hallucinations [86].
Bereavement	VH of the deceased can occur as part of normal grief reaction but are less frequent than sensed presence of the deceased [87]
Delirium	VH are the commonest modality of hallucination in delirium [88] where they occur in the context of clouded consciousness, sleep dysregulation and affective symptoms.
Sleep-related	Occasional VH can be normal experiences at the margins of sleep (hypnagogic / hypnopompic hallucinations). They may also present as part of a sleep-disorder (e.g. narcolepsy).
Medication side effects	PD medication can precipitate VH but the exact mechanism and its relation to PD neurodegeneration is unclear [35]. Medication with anti-muscarinic effects and opiates are particularly implicated in VH.
Hallucinogen use	Visual perceptual phenomena including persistent visual snow (see below) afterimages, palinopsia and flashback VH may persist after hallucinogen exposure (Hallucinogen Persisting Perception Disorder – HPPD) [89].
Peduncular hallucinations	Complex visual hallucinations caused by brainstem or thalamic lesions [90]. When caused by brainstem lesions, VH are associated with sleep disturbance and eye movement dysfunction. Hallucinations in other modalities can occur.
Occipital / temporal seizures	Ictal phenomenology is based on location of seizure. Simple VH are associated with occipital foci [91]. Complex VH imply involvement of the temporal lobe and limbic cortex [92].
Migraine	Teichopsia in classical migraine aura and other visual perceptual phenomena [93].
Visual snow syndrome	A syndrome characterised by persistent dynamic visual noise (snow), palinopsia, entopic phenomena, photophobia and nyctalopia [94]. Associated with migraine.

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; PD = Parkinson's disease; PDD Parkinson's disease dementia, VaD = vascular dementia VH= Visual hallucinations

Case identification

Whatever the underlying condition, help can only be provided for patients with VH if these symptoms have been identified by their clinical team. The workgroup identified the need to address continuing stigma of self-reporting symptoms perceived as indicators of mental illness or dementia. Evidence from eye disease that pre-emptive warning may be effective in reducing distress or emotional impact at VH onset [41] suggests that that low-level information about the possible future occurrence of VH should be provided at the point of eye disease, dementia or PD diagnosis, with signposting to more detailed information which can be accessed at a later stage. Systematic enquiry about the occurrence of VH should be part of routine follow-up to help share responsibility for identifying VH between the patient and care team.

Threshold for specific treatment intervention

The workgroup noted that VH that are not distressing for the patient or carer do not need treatment beyond general measures, psycho-education and help in adapting, accepting and living well with symptoms. Typically, this benign VH phase occurs early in the disease, highlighting the importance of keeping VH under review. An important factor defining the threshold at which intervention is required may be the transition from full insight to partial or fluctuating insight, where the patient responds to VH as if they are real at the time they occur, even if insight is restored after the event. This insight-related phenomenological distinction corresponds to that in the neurological literature between pseudohallucinations (defined by intact insight) and hallucinations without insight. The terminology is unsatisfactory as pseudohallucinations carry different implications in the psychiatric literature; however, the conceptual distinction between VH with insight intact in contrast to partial, fluctuating and absent insight states is worth revisiting as it helps mark a transition point for treatment need in all conditions. The workgroup also noted exceptions to the association between insight and treatment need, for example, intervention might be required in the presence of full, continuous insight where VH content is itself distressing or VH become so intrusive they limit function.

Carers and VH

Another feature of VH common to different conditions is the need to also consider their impact on carers. Factors mediating the increased risk of care home placement with VH are unclear but may include carer distress caused indirectly by VH. The consensus view was that the treatment of VH should extend beyond the patient to provide support and advice for the carer.

Consensus framework for the management of VH

The general framework for managing VH and related symptoms is summarised in Figure 1. It begins before the onset of hallucinations with forewarning and pre-emptive questioning to encourage their reporting. Once VH are identified, a staged approach is suggested with a review of cognitive and ophthalmological health as well as a physical health / delirium screen. Medication should be reviewed, focussing on anti-muscarinic and opiate drugs and, in PD, dopaminergic therapy. Support including reassurance, psycho-education, normalisation (explaining VH are part of a disease and have a basis in brain function) and optimisation of visual functioning should be offered. This should be person-centred, identifying the particular triggers and settings that increase the risk of VH and avoiding these situations by planning alternative meaningful and rewarding activities.

VH that become clinically significant by causing distress to the patient or their carers require further intervention. Given limitations in both understanding of the underlying mechanism(s) of VH susceptibility or the neurophysiological changes coincident with VH and the clinical trial evidence base, the workgroup were unable to make definitive medication recommendations. There is a theoretical basis for pharmacological interventions targeting cholinergic, GABAergic, serotonergic or dopaminergic systems and for reducing cortical excitability through non-invasive stimulation or anticonvulsant medication. Treatment might aim to reverse long-term changes associated with VH susceptibility or to reduce the frequency or duration of transient changes co-incident with VH.

Future directions

The working group noted an important methodological challenge for clinical trials or mechanistic studies is the lack of accepted, validated, rating scales for VH or related symptoms. There is a clear need to develop better metrics which extend beyond retrospective collection of questionnaire or scale data to real-world collection of VH as they occur using, for example, new mobile technology or real-time functional data through developments in EEG telemetry. Measures of VH susceptibility are also required, such as pareidolia tests developed for DLB [95, 96]. Given the importance of insight and its continuity at the decision point for specific intervention, better measures of insight which are sensitive to partial or fluctuating states are required, as well as studies of the cognitive context in which insight becomes impaired, for example, generalised cognitive decline or decline in specific cognitive functions such as self-monitoring or symptom-awareness [97].

For clinical trials, the workgroup highlighted the lack of standardisation of VH-related outcome measures and the need for trials taking a trans-diagnostic, mechanism-based perspective to complement evidence from the traditional condition-specific trials. It remains to be established whether a single treatment approach will be effective in all conditions or whether different

treatments will be required with further studies needed of the underlying mechanism of VH from a trans-diagnostic perspective and the role of dysfunction in distributed brain networks. Clinical trials for non-pharmacological approaches are also required, in particular the role of psychological therapies such as re-scripting, imagery transformation, desensitisation, CBT targeting patient-carer dyads and non-invasive brain stimulation. Both medication and non-pharmacological trials might target longer-term susceptibility or transient changes, either separately or in combination.

Conclusions

Although the clinical importance of VH and related symptoms has long been recognised, the evidence-base for their mechanism or treatment is limited and focuses on single conditions. A wider perspective is required, highlighting key similarities and differences between conditions and taking into account brain changes conferring susceptibility to such symptoms as well as those co-incident with their occurrence. In advance of such developments, the workgroup concluded that treatment of VH, irrespective of their clinical context, would benefit from a common management framework and shared priorities for future research.

Author's contributions

John O'Brien wrote the first draft with John-Paul Taylor and Dominic ffytche. All other authors attended and contributed to the SHAPED workshop where the evidence was reviewed and discussed. All authors then contributed to the final drafts of the manuscript and approved the final version.

Competing Interests

Roger A Barker has acted as a consultant to UCB, Living Cell Technologies, BlueRock Therapeutics, Sana Biotechnology, FCDI, Novo Nordisk and Cellino.

Clare Bradley is director and majority shareholder of Health Psychology Research Ltd, which licences her patient-reported outcome measures for others to use and manages their linguistic validation into other languages. She receives royalties when existing language versions of her questionnaires are licensed to commercial companies. Her College currently receives research grants to support her research from ViiVHealthCare and from Medtronic. She has recently received speaker fees from Astellas and routinely advises many pharmaceutical companies and contract research organisations on the use of her questionnaires in their clinical trials.

Robert Dudley reports delivering training workshops and has written books about CBT, for which he has received fees, and reports delivering CBT in the National Health Service (NHS).

Paul Francis has received speaking fees from Suven and Nutricia.

Iracema Leroi has received speaking fees from Eisai, Boehringer Ingelheim, GE Healthcare, GlaxoSmithKline, Shire, and Lundbeck.

Ian McKeith has acted as a consultant for GE Healthcare, Sumitomo Dainippon Pharma, Sanofi and Eisai.

John O'Brien has acted as a consultant for TauRx, Axon, GE Healthcare and Eisai.

Marco Onofrj has served on the scientific advisory boards of GlaxoSmithKline, Novartis, Lundbeck, Eisai, Valeant, Medtronic, and Newron; has received speaker honoraria from Zambon, the World Parkinson Congress, the Movement Disorder Society, and the Atypical Dementias congress; was an invited guest and lecturer for the Mental Disorders in Parkinson Disease Congress; serves on the editorial board of Medicine (Baltimore); has been employed as a speaker for Boehringer Ingelheim,

GlaxoSmithKline, UCB, and Zambon; and has received research support from the Italian Ministry of Health and the Italian Ministry of Education.

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Figure legend

Figure 1. The consensus framework for the management of visual hallucinations in different conditions. Recommendations not supported by meta-analysis are indicated in white. Orange boxes indicate hallucination characteristics and therapeutic targets.

References

1. Cummings, J., et al., *Pimavanserin: Potential Treatment For Dementia-Related Psychosis.* J Prev Alzheimers Dis, 2018. **5**(4): p. 253-258.
2. McKeith, I.G., et al., *Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium.* Neurology, 2017. **89**(1): p. 88-100.
3. ffytche, D.H., *Visual hallucinations in eye disease.* Curr Opin Neurol, 2009. **22**(1): p. 28-35.
4. Gibson, G., et al., *Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study.* Int J Geriatr Psychiatry, 2013. **28**(6): p. 626-31.
5. ffytche, D.H., et al., *The anatomy of conscious vision: an fMRI study of visual hallucinations.* Nature Neuroscience, 1998. **1**(8): p. 738-742.
6. Stebbins, G.T., et al., *Altered cortical visual processing in PD with hallucinations: an fMRI study.* Neurology, 2004. **63**(8): p. 1409-16.
7. Collerton, D., E. Perry, and I. McKeith, *Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations.* Behav Brain Sci, 2005. **28**(6): p. 737-57; discussion 757-94.
8. Shine, J.M., et al., *Tricks of the mind: Visual hallucinations as disorders of attention.* Prog Neurobiol, 2014. **116**: p. 58-65.
9. Zarkali, A., et al., *Increased weighting on prior knowledge in Lewy Body-associated visual hallucinations.* Brain Communications, 2019.
10. Burke, W., *The neural basis of Charles Bonnet hallucinations: a hypothesis.* Journal of Neurology, Neurosurgery and Psychiatry (London), 2002. **73**: p. 535-541.
11. Allen, P., et al., *The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations.* Neurosci Biobehav Rev, 2008. **32**(1): p. 175-91.
12. Carter, R. and D.H. ffytche, *On visual hallucinations and cortical networks: a trans-diagnostic review.* J Neurol, 2015. **262**(7): p. 1780-90.
13. Boes, A.D., et al., *Network localization of neurological symptoms from focal brain lesions.* Brain, 2015. **138**(Pt 10): p. 3061-75.
14. Tiraboschi, P., et al., *What best differentiates Lewy body from Alzheimer's disease in early-stage dementia?* Brain, 2006. **129**(Pt 3): p. 729-35.
15. Toledo, J.B., et al., *Clinical and multimodal biomarker correlates of ADNI neuropathological findings.* Acta Neuropathol Commun, 2013. **1**: p. 65.
16. Harding, A.J., G.A. Broe, and G.M. Halliday, *Visual hallucinations in Lewy Body disease relate to Lewy bodies in the temporal lobe.* Brain, 2002. **125**: p. 391-403.
17. Gallagher, D.A., et al., *Testing an aetiological model of visual hallucinations in Parkinson's disease.* Brain, 2011. **134**(Pt 11): p. 3299-309.
18. Papapetropoulos, S., et al., *Cortical and amygdalar Lewy body burden in Parkinson's disease patients with visual hallucinations.* Parkinsonism Relat Disord, 2006. **12**(4): p. 253-6.
19. Harding, A.J., et al., *Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease.* Brain, 2002. **125**(Pt 11): p. 2431-45.
20. Jacobson, S.A., et al., *Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations.* Parkinsonism Relat Disord, 2014. **20**(9): p. 1009-14.
21. ffytche, D.H., et al., *Risk factors for early psychosis in PD: insights from the Parkinson's Progression Markers Initiative.* J Neurol Neurosurg Psychiatry, 2017. **88**(4): p. 325-331.
22. Kalaitzakis, M.E., et al., *Dementia and visual hallucinations associated with limbic pathology in Parkinson's disease.* Parkinsonism Relat Disord, 2009. **15**(3): p. 196-204.
23. Court, J.A., et al., *Visual hallucinations are associated with lower alpha bungarotoxin binding in dementia with Lewy bodies.* Pharmacol Biochem Behav, 2001. **70**(4): p. 571-9.
24. Hepp, D.H., et al., *Pedunculopontine cholinergic cell loss in hallucinating Parkinson disease patients but not in dementia with Lewy bodies patients.* J Neuropathol Exp Neurol, 2013. **72**(12): p. 1162-70.
25. Satoh, M., et al., *Improved Visual Hallucination by Donepezil and Occipital Glucose Metabolism in Dementia with Lewy Bodies: The Osaki-Tajiri Project.* European Neurology, 2010. **64**(6): p. 337-344.
26. Teaktong, T., et al., *Muscarinic M2 and M4 receptors in anterior cingulate cortex: relation to neuropsychiatric symptoms in dementia with Lewy bodies.* Behav Brain Res, 2005. **161**(2): p. 299-305.

27. Bullock, R. and A. Cameron, *Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: a case series.* Curr Med Res Opin, 2002. **18**(5): p. 258-64.
28. Sobow, T., *Parkinson's disease-related visual hallucinations unresponsive to atypical antipsychotics treated with cholinesterase inhibitors: a case series.* Neurol Neurochir Pol, 2007. **41**(3): p. 276-9.
29. Kurita, A., et al., *The beneficial effect of donepezil on visual hallucinations in three patients with Parkinson's disease.* J Geriatr Psychiatry Neurol, 2003. **16**(3): p. 184-8.
30. Burn, D., et al., *Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease.* Mov Disord, 2006. **21**(11): p. 1899-907.
31. Vermeiren, Y., et al., *Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia.* Alzheimers Dement, 2013. **9**(5): p. 488-98.
32. Ravina, B., et al., *Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease.* Mov Disord, 2012. **27**(11): p. 1392-7.
33. Jaakkola, E., et al., *Ventral striatal dopaminergic defect is associated with hallucinations in Parkinson's disease.* Eur J Neurol, 2017. **24**(11): p. 1341-1347.
34. Kiferle, L., et al., *Caudate dopaminergic denervation and visual hallucinations: evidence from a (1)(2)(3)I-FP-CIT SPECT study.* Parkinsonism Relat Disord, 2014. **20**(7): p. 761-5.
35. Dave, S., et al., *Drug and Disease Effects in Parkinson's Psychosis: Revisiting the Role of Dopamine.* Mov Disord Clin Pract, 2020. **7**(1): p. 32-36.
36. Khundakar, A.A., et al., *Analysis of primary visual cortex in dementia with Lewy bodies indicates GABAergic involvement associated with recurrent complex visual hallucinations.* Acta Neuropathologica Communications, 2016. **4**(1): p. 66.
37. Huot, P., et al., *Increased 5-HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations.* Mov Disord, 2010. **25**(10): p. 1399-408.
38. Ballanger, B., et al., *Serotonin 2A receptors and visual hallucinations in Parkinson disease.* Arch Neurol, 2010. **67**(4): p. 416-21.
39. Abbott, E.J., et al., *Visual loss and visual hallucinations in patients with age-related macular degeneration (Charles Bonnet syndrome).* Invest Ophthalmol Vis Sci, 2007. **48**(3): p. 1416-23.
40. Santhouse, A.M., R.J. Howard, and D.H. ffytche, *Visual hallucinatory syndromes and the anatomy of the visual brain.* Brain, 2000. **123**: p. 2055-2064.
41. Cox, T.M. and D.H. ffytche, *Negative outcome Charles Bonnet syndrome.* Br J Ophthalmol, 2014. **98**(9): p. 1236-9.
42. Menon, G.J., *Complex visual hallucinations in the visually impaired: a structured history-taking approach.* Arch Ophthalmol, 2005. **123**(3): p. 349-55.
43. Scott, I.U., et al., *Visual hallucinations in patients with retinal disease.* American Journal of Ophthalmology, 2001. **131**: p. 590-598.
44. Crumbliss, K.E., M.J. Taussig, and W.M. Jay, *Vision rehabilitation and Charles Bonnet Syndrome.* Semin Ophthalmol, 2008. **23**(2): p. 121-6.
45. Jefferis, J.M., M.P. Clarke, and J.P. Taylor, *Effect of cataract surgery on cognition, mood, and visual hallucinations in older adults.* J Cataract Refract Surg, 2015. **41**(6): p. 1241-7.
46. Singh, A. and T.L. Sørensen, *Charles Bonnet syndrome improves when treatment is effective in age-related macular degeneration.* British Journal of Ophthalmology, 2011. **95**(2): p. 291-292.
47. Holroyd, S. and S. Sabeen, *Successful treatment of hallucinations associated with sensory impairment using gabapentin.* J Neuropsychiatry Clin Neurosci, 2008. **20**(3): p. 364-6.
48. Hosty, G., *Charles Bonnet syndrome: a description of two cases.* Acta Psychiatr Scand, 1990. **82**(4): p. 316-7.
49. Burke, W.J., W.H. Roccaforte, and S.P. Wengel, *Treating visual hallucinations with donepezil.* American Journal of Psychiatry, 1999. **156**: p. 1117-1118.
50. Nevins, M., *Charles Bonnet syndrome.* J Am Geriatr Soc, 1997. **45**(7): p. 894-5.
51. Bergman, Y. and Y. Barak, *Escitalopram for antipsychotic nonresponsive visual hallucinosis: eight patients suffering from Charles Bonnet syndrome.* Int Psychogeriatr, 2013. **25**(9): p. 1433-6.
52. Maeda, K., et al., *Charles Bonnet syndrome with visual hallucinations of childhood experience: successful treatment of 1 patient with risperidone.* J Clin Psychiatry, 2003. **64**(9): p. 1131-2.
53. Miyaoka, T., et al., *Yi-gan san for treatment of charles bonnet syndrome (visual hallucination due to vision loss): an open-label study.* Clin Neuropharmacol, 2011. **34**(1): p. 24-7.
54. Merabet, L.B., et al., *Suppression of complex visual hallucinatory experiences by occipital transcranial magnetic stimulation: a case report.* Neurocase, 2003. **9**(5): p. 436-40.

55. ffytche, D.H., et al., *The psychosis spectrum in Parkinson disease.* Nat Rev Neurol, 2017. **13**(2): p. 81-95.
56. Goetz, C.G. and G.T. Stebbins, *Mortality and hallucinations in nursing home patients with advanced Parkinson's disease.* Neurology, 1995. **45**: p. 669-671.
57. Weintraub, D., et al., *Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease.* JAMA Neurol, 2016. **73**: p. 535-541.
58. Goetz, C.G. and G.T. Stebbins, *Risk factors for nursing home placement in advanced Parkinson's disease.* Neurology, 1993. **43**: p. 2227-2229.
59. Renouf, S., et al., *Visual hallucinations in dementia and Parkinson's disease: A qualitative exploration of patient and caregiver experiences.* Int J Geriatr Psychiatry, 2018. **33**(10): p. 1327-1334.
60. McKinlay, A., et al., *A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia.* Parkinsonism Relat Disord, 2008. **14**(1): p. 37-42.
61. NICE, *Parkinson's disease in adults*. 2017.
62. Diederich, N.J., V. Pieri, and C.G. Goetz, *Coping strategies for visual hallucinations in Parkinson's disease.* Mov Disord, 2003. **18**(7): p. 831-2.
63. Mueller, C., et al., *Assessment and Management of Neuropsychiatric Symptoms in Parkinson's Disease.* CNS Drugs, 2018. **32**(7): p. 621-635.
64. Connolly, B.S. and A.E. Lang, *Pharmacological treatment of Parkinson disease: a review.* JAMA, 2014. **311**(16): p. 1670-83.
65. Diederich, N.J., et al., *Hallucinations in Parkinson disease.* Nat Rev Neurol, 2009. **5**(6): p. 331-42.
66. Wilby, K.J., et al., *Evidence-Based Review of Pharmacotherapy Used for Parkinson's Disease Psychosis.* Ann Pharmacother, 2017. **51**(8): p. 682-695.
67. Pollak, P., et al., *Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up.* J Neurol Neurosurg Psychiatry, 2004. **75**(5): p. 689-95.
68. Parkinson study group, *Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group.* N Engl J Med, 1999. **340**(10): p. 757-63.
69. Ondo, W.G., et al., *Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease.* Mov Disord, 2005. **20**(8): p. 958-63.
70. Shotbolt, P., et al., *A randomized controlled trial of quetiapine for psychosis in Parkinson's disease.* Neuropsychiatr Dis Treat, 2009. **5**: p. 327-32.
71. Rabey, J.M., et al., *Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration.* Mov Disord, 2007. **22**(3): p. 313-8.
72. Fernandez, H.H., et al., *Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study.* Int J Neurosci, 2009. **119**(12): p. 2196-205.
73. Meltzer, H.Y., et al., *Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis.* Neuropsychopharmacology, 2010. **35**(4): p. 881-92.
74. Cummings, J., et al., *Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial.* Lancet, 2014. **383**(9916): p. 533-40.
75. Urwyler, P., et al., *Visual Hallucinations in Eye Disease and Lewy Body Disease.* Am J Geriatr Psychiatry, 2016. **24**(5): p. 350-8.
76. Collerton, D. and J.P. Taylor, *Advances in the treatment of visual hallucinations in neurodegenerative diseases.* Future Neurol, 2013. **8**(4): p. 433-444.
77. Hope, T., et al., *Natural history of behavioural changes and psychiatric symptoms in Alzheimer's disease. A longitudinal study.* Br J Psychiatry, 1999. **174**: p. 39-44.
78. Stern, Y., et al., *Predicting time to nursing home care and death in individuals with Alzheimer disease.* JAMA, 1997. **277**(10): p. 806-12.
79. Tampi, R.R., et al., *Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses.* Therapeutic Advances in Chronic Disease, 2016. **7**(5): p. 229-245.
80. Pakrasi, S., et al., *Cholinesterase inhibitors in advanced Dementia with Lewy bodies: increase or stop?* International Journal of Geriatric Psychiatry, 2006. **21**(8): p. 719-721.
81. Emre, M., et al., *Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial.* Lancet Neurol, 2010. **9**(10): p. 969-77.
82. Elder, G.J., et al., *Consecutive sessions of transcranial direct current stimulation do not remediate visual hallucinations in Lewy body dementia: a randomised controlled trial.* Alzheimers Res Ther, 2019. **11**(1): p. 9.

83. Skogseth, R., et al., *Accuracy of Clinical Diagnosis of Dementia with Lewy Bodies versus Neuropathology.* J Alzheimers Dis, 2017. **59**(4): p. 1139-1152.
84. Russell, G. and A. Burns, *Charles Bonnet syndrome and cognitive impairment: a systematic review.* Int Psychogeriatr, 2014. **26**(9): p. 1431-1443.
85. Chapman, F.M., et al., *Associations among visual hallucinations, visual acuity and specific eye pathologies in Alzheimer's disease.* American Journal of Psychiatry, 1999. **156**: p. 1983-1985.
86. Waters, F., et al., *Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease.* Schizophr Bull, 2014. **40 Suppl 4**: p. S233-45.
87. Rees, W.D., *The hallucinations of widowhood.* British Medical Journal, 1971. **4**: p. 37-41.
88. Webster, R. and S. Holroyd, *Prevalence of psychotic symptoms in delirium.* Psychosomatics, 2000. **41**(6): p. 519-22.
89. Halpern, J.H. and H.G. Pope, Jr., *Hallucinogen persisting perception disorder: what do we know after 50 years?* Drug Alcohol Depend, 2003. **69**(2): p. 109-19.
90. Benke, T., *Peduncular hallucinosis: a syndrome of impaired reality monitoring.* J Neurol, 2006. **253**(12): p. 1561-71.
91. Panayiotopoulos, C.P., *Elementary visual hallucinations, blindness, and headache in idiopathic occipital epilepsy: differentiation from migraine.* J Neurol Neurosurg Psychiatry, 1999. **66**(4): p. 536-40.
92. Gloor, P., et al., *The role of the limbic system in experiential phenomena of temporal lobe epilepsy.* Ann Neurol, 1982. **12**(2): p. 129-44.
93. Klee, A. and R. Willanger, *Disturbances of visual perception in migraine.* Acta Neurologica Scandinavica, 1966. **42**: p. 400-414.
94. Schankin, C.J., et al., *'Visual snow' - a disorder distinct from persistent migraine aura.* Brain, 2014. **137**(Pt 5): p. 1419-28.
95. Yokoi, K., et al., *Hallucinators find meaning in noises: pareidolic illusions in dementia with Lewy bodies.* Neuropsychologia, 2014. **56**: p. 245-54.
96. Uchiyama, M., et al., *Pareidolias: complex visual illusions in dementia with Lewy bodies.* Brain, 2012. **135**(Pt 8): p. 2458-69.
97. Shad, M.U., et al., *Neurobiological underpinnings of insight deficits in schizophrenia.* Int Rev Psychiatry, 2007. **19**(4): p. 437-46.